REMARKS

Claims 9-10, 16-17, 20-24, 26-27 and 30-38 are in the case.

Claims 9, 16-17, 20-24, 26-27 and 30-33 are amended herein. Support for these amendments can be found in the application as filed.

Claims 1-8, 11-15, 18-19, 25 and 29 are cancelled.

Claims 34 to 38 are new. Support for new claims 34-38 reciting devices may be found in original claim 3, at page 6, line 16 in Example 1 and at page 15, line 24 in Example 2 for the catheter, and at page 24, lines 26 to 27 for the stent.

No new matter has been added. Reconsideration of this Application and entry of the foregoing amendments are requested.

REJECTIONS UNDER 35 U.S.C. § 102(b)

Claims 9 and 24 were rejected as being anticipated over Dai-Do et al. ("Dai Do") under 35 U.S.C. § 102(b).

Claims 9-10, 18-19, 24 and 28-29 are rejected as being anticipated over U.S. Patent No 5,866,561 to Mark T. Ungs ("Ungs").

Applicant respectfully traverses the rejection as follows.

Neither Dai Do nor Ungs disclose the *in vivo* dosage recited in claims 9, 24 and 34.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw this rejection.

REJECTION UNDER 35 U.S.C. § 103(a)

Claims 22-23 and 32-33 are rejected as being obvious over U.S. Patent No 5,866,561 to Mark T. Ungs ("Ungs") under 35 U.S.C. § 103(a).

Claims 15-17, 20-21, 25-27 and 30-31 are rejected as being obvious over Ungs and in view of U.S. Patent No 5,512,557 to Peter Collins ("Collins") under 35 U.S.C. § 103(a).

Applicant respectfully disagrees for the following reasons.

It is first respectfully submitted that Collins discloses daily doses of estradiol for oral/systemic administration in the treatment of myochardial ischaemia. In contrast, the method of the present invention comprises a dosage to be administered not daily but once with a device for intracoronary delivery to reduce restenosis. Collins himself acknowledges that "[t]he dosage may be varied depending on the symptoms, age and body weight of the patients, ***the route of administration and the form of the preparation***" (see col. 2, lines 16-18). It may of course be further added that dosage may also be varied depending on the condition to be treated. It is submitted that a person of ordinary skill in the art understood at the time of the invention that daily dosages as those described in Collins were not necessarily appropriate for single *in situ* administration to reduce restenosis and that person would not have been motivated to use such dosages. Collins' disclosed daily estradiol doses for systemic administration were thus not predictive of the ability of the claimed dosage to reduce restenosis through *in situ* administration. Ungs does not suggest a specific dosage for administering

estradiol *in situ*. It is thus submitted that Collins in combination with Ungs does not make the dosage recited in the present application obvious.

It is further respectfully submitted that in determining obviousness, §103(a) expressly requires considering the claimed invention "as a whole". The Examiner is reminded that focusing the §103(a) inquiry on a particular aspect of the invention that differs from the prior art improperly disregards the "as a whole" statutory mandate. See *Hybritech, Inc.* v. *Monoclonal Antibodies, Inc.*, 802 F .2d 1367, 1383, 231 U.S.P.Q. 81 93 (Fed. Cir. 1986) "Focusing on the obviousness of substitutions and differences instead of on the invention as a whole, as the district court did in frequently describing the claimed invention as a mere substitution of monoclonal for polyclonal antibodies in a sandwich assay, was a legally improper way to simplify the difficult determination of obviousness."

As a whole, Applicant's invention is a method for reducing restenosis comprising administering estradiol with a device at the injured site of a vessel in an single dosage able to reduce restenosis.

To the Applicant's knowledge, the Applicant is the first to have performed such intervention and to have demonstrated that it works. The Examiner has not established that a person of ordinary skill in the art at the time of the invention would have reasonably expected the claimed invention to work.

It is submitted that estradiol's reported *in vitro* effects on vascular smooth muscle cell proliferation and/or migration were not predictive of its effect in the claimed dosage at the injured site of a vessel *in vivo*. In fact, the teachings regarding estradiol's ability to reduce proliferation of vascular smooth muscle cells were contradictory prior to the Applicant's invention as recognized by Dai Do et al. (of record) "*Experiments with cultured vascular smooth muscle cells obtained from rats and pigs, however revealed inconsistent antiproliferative effects of 17β-estradiol*" (see page 983, right column, lines 21-24).

It is respectfully submitted that none of the cited references alone or in combination disclose or suggest with an expectation of success that estradiol could be administered with a device at an injured site of a vessel for effectively reducing restenosis.

DOUBLE PATENTING

Claims 9-10 and 15-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-4 and 8-23 of co-pending application No. 10/088,405 in view of Ungs.

The Examiner states that "one of ordinary skill in the art would find it obvious to apply the reendothelization and vascular endothelial function improving method of the co-pending application for the reduction of restenosis, as in the instant claims, with the expectation that the method that improves the vascular endothelial growth and function would also inhibit restenosis" (last 5 lines of first paragraph of page 11 of the instant Office Action).

Respectfully, the Applicant disagrees and refers the Examiner to the enclosed Declaration and Curriculum Vitae of Dr. Richard Stack, which was originally submitted to the Japanese Patent Office during the prosecution of the Japanese counterpart of the present application. Dr. Stack's Declaraton is cited as support for the fact that restenosis and reendothelization are two independent events that are affected differently by different compounds. However, to speed prosecution, a terminal disclaimer is included to accelerate allowance of the present case.

The rejections of the original claims are believed to have been overcome by the present remarks and the introduction of new claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited.

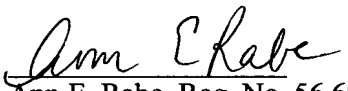
The Commissioner is authorized to charge any fees under 37 CFR §1.17 that may be due on this application to Deposit Account 17-0055. The Commissioner is also authorized to treat this amendment and any future reply in this matter requiring a petition for an extension of time as incorporating a petition for extension of time for the appropriate length of time as provided by 37 CFR §136(a)(3).

Respectfully submitted,

Institut de Cardiologie de Montréal (ICM)

by: Quarles and Brady, LLP

Date: September 29, 2006



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